Is There Any Objective Improvement of Nocturia by Combination Treatment of Zolpidem and Alpha-Blocker Therapy for Unresponsive to Alpha-Blocker Monotherapy in Men with Lower Urinary Tract Symptoms?

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Objectives: The aim of the present study was to determine whether administration of zolpidem, a nonbenzodiazepine sedative-hypnotic agent, at night would improve the nocturia unresponsive to alpha-blocker monotherapy in men with lower urinary tract symptoms (LUTS).

Methods: This was a prospective observational study comprised of 39 men aged 50 years and older. The study inclusion criteria were age more than 50 years, and nocturia twice or more per night after taking alpha-blockers for more than 8 weeks. A total of 39 patients met the criteria and constituted the study cohort. Pittsburgh Sleep Quality Index (PSQI), International Prostate Symptom Score (IPSS), frequency volume chart (FVCs) and uroflowmetry were recorded. Patients were given 10 mg alfuzosin and 10 mg zolpidem once at night for the 8 weeks.

Results: There were no serious side-effects in any patient. Nocturia decreased from a baseline (3.1 ± 0.1) to 8 weeks (1.6 ± 0.2) (P = 0.001). After treatment, global PSQI scores and severe sleep disorders improved. Storage and voiding symptoms including total IPSS scores and quality of life index improved. Nocturnal urine volume and functional bladder capacity improved. Maximum flow rate, voided volume increased and residual urine volume decreased.

Conclusion: Combined zolpidem and alpha-blocker therapy resulted in a subjective and objective reduction in nocturia episodes when given to men with nocturia unresponsive to alpha-blocker monotherapy.

Key words alpha-blocker, lower urinary tract symptom, male, nocturia, zolpidem

1. INTRODUCTION

Bladder outlet obstruction (BOO) followed by benign prostatic hyperplasia (BPH) can induce bladder overactivity and a decrease of functional bladder capacity. Nocturia may be developed and is one of the most bothersome lower urinary tract symptoms (LUTS). It may result in daytime fatigue, a lower level of general wellbeing and the risk of nightly falls.

Nocturia responds less successfully to medical or surgical treatment than do other LUTS. The causes of nocturia are urine overproduction, decreased functional bladder capacity, or a combination of both factors.

Loss of normal circadian rhythms may induce sleep disturbance at night. When a person awakes from sleep due to sleep disturbance at night, they may feel the need to void. Decrease of nocturnal production of melatonin may induce sleep disturbance and administration of melatonin at night improved the symptoms of nocturia in elderly people. Thus, medications that assist sleep may improve nocturia. We reported that combined medication of zolpidem, a nonbenzodiazepine sedative-hypnotic agent and alpha-blocker resulted in reduction of nocturia episodes when given to some men unresponsive to alpha-blocker monotherapy with LUTS. However, it resulted in a subjective reduction using IPSS questionnaire alone and objective evidences such as frequency-volume charts (FVCs) and sleep quality index are required.

FVCs are one of the most important methods for objectively assessing voiding patterns. The FVC provides not only the frequency of voiding, but also urinary volume per void and total urinary volume during the day or night. Based on such data it is possible to classify the cause of nocturia such as nocturnal polyuria or detrusor overactivity. The Pittsburgh Sleep Quality Index (PSQI) is a worldwide used questionnaire of the sleep quality and it is possible to assess the sleep quality in men with lower urinary tract symptoms.

This study was the first study to investigate to determine whether combination therapy of zolpidem and alpha-blocker at night would improve the frequency...
of nocturia subjectively and objectively unresponsive to
alpha-blocker monotherapy in men with LUTS.

2. METHODS

2.1. Patient selection

Approval for this study was obtained from the Internal Review Board at the Hospital and informed consent was obtained from each patient. Between September 2008 and August 2010, consecutive men presenting with LUTS were recruited into this prospective study. The study inclusion criteria were age more than 50 years with LUTS, and nocturia twice or more per night after taking alpha-blockers for more than 8 weeks. Exclusion criteria included use of medications for control of bladder symptoms, use of sedatives or tranquilizers for treating sleep disturbances, bladder tumors, bladder stones, urethral strictures, neurogenic bladder dysfunction, restricted mobility, and working primarily at night. Patients were also excluded from the analysis if they had a documented history or clinical symptoms of prostatitis, prostate cancer, or prostatic intraepithelial neoplasia on biopsy, serum prostate-specific antigen (PSA) levels over 20 ng/mL, history of prostate surgery or radiotherapy, acute urinary retention or an indwelling catheter, evidence of acute urinary infection (pyuria and bacteriuria) on urine analysis, or if they had ever taken 5-alpha-reductase inhibitors.

Of the consecutive patients, 39 met the criteria and constituted the study cohort. The mean age of the study patients was 62.9 ± 1.1 years, their mean total prostate and transition zone volumes were 30.3 ± 1.4 and 13.5 ± 1.1 mL, respectively, and their mean PSA level was 1.48 ± 0.33 ng/mL. All patients were given 10 mg alfuzosin once daily and 10 mg zolpidem once at night for 8 weeks.

2.2. Methodology

This was a prospective observational study. One investigator conducted face-to-face interviews with all study participants using a structured questionnaire. At the initial visit, the patients underwent a detailed clinical evaluation, including a complete history, physical examination, International Prostate Symptom Score (IPSS) questionnaire, urine analysis, urine culture, digital rectal examination (DRE), and estimates of serum PSA level, prostate volume by transrectal ultrasonography (TRUS), uroflowmetry and postvoid residual urine volume (PVR) and IPSS. Patients were asked to measure and record the time and volume of each void for at least three consecutive days. Each of the patients received two beakers (graduated in 10-mL increments) and was instructed how to complete the 3-day FVCs, including 24-h urine volume, nocturnal urine volume (NUV), functional bladder capacity (FBC), nocturnal polyuria index (NPi), and nocturnal bladder capacity index (NBCi). Twenty-four-hour urine volume over 2500 mL was classified as polyuria. NPi over 0.35 was classified as nocturnal polyuria. NBCi over 2 was classified to low nocturnal bladder capacity.

Uroflowmetry was conducted, with measurements of PVR by abdominal ultrasonography. Maximum urinary flow rate (Qmax), voided volume, and PVR were all assessed both at baseline and at the end of the treatment period. LUTS and symptom-specific quality of life (QoL) were assessed using the IPSS and the associated QoL score at baseline and at the end of the treatment period. Frequency of nocturia was assessed at baseline, before zolpidem and alpha-blocker combination treatment, and 8-week zolpidem and alpha-blocker combination treatment period. Sleep quality was assessed using PSQI.

The primary endpoint of the study was the evaluation of objective improvement by assessing FVC and uroflowmetry. The secondary endpoint was the evaluation of subjective improvement of LUTS and sleep quality by assessing the IPSS and PSQI. Twenty-one patients with nocturia (53.8%) had associated diseases, including hypertension in 9 (23.1%), diabetes in 7 (17.9%), and hyperlipidemia in 5 (12.8%).

Cognitive or psychomotor adverse events, including drowsiness, sensory disturbances, hallucinations, nightmares, psychosis, ataxia, tachycardia, dizziness, confusion, unpleasant taste and gastrointestinal problems were examined at 8 weeks during an interview, when participants were asked whether they had any untoward reactions since the previous study visit.

2.3. Data analysis

A frequency analysis was carried out to estimate the average of each variable. Paired t-test was used to explain the differences between the variables at baseline and 8 weeks. All data were expressed as mean ± SE, and SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical processing. Differences were considered to be statistically significant when \( P < 0.05 \).

3. RESULTS

3.1. Number of nocturia

Nocturia decreased from baseline (3.1 ± 0.1) to 8 weeks after taking zolpidem and alpha-blockers (1.6 ± 0.2) on the IPSS (\( P = 0.001 \)).

3.2. Cause of nocturia

Polyuria, nocturnal polyuria and low nocturnal bladder capacity were found in 17.9% (7 of 39 patients), 23.1% (9 of 39 patients) and 59.0% (23 of 39 patients), respectively.

3.3. IPSS

At 8 weeks after taking combined zolpidem and alpha-blockers, storage and voiding symptoms, including total IPSS scores significantly decreased compared with baseline. QoL index decreased significantly from baseline (4.2 ± 0.1) to 8 weeks after taking combined zolpidem and alpha-blockers (2.9 ± 0.3) (Fig. 1).

3.4. FVCs

Twenty-four-hour urine volume decreased from baseline (2028.6 ± 147.6 mL) to 8 weeks after taking zolpidem and alpha-blockers (1837.1 ± 205.9, \( P > 0.05 \)). Nocturnal
urine volume decreased from baseline \((639.6 \pm 80.0 \text{ mL})\) to 8 weeks after taking zolpidem and alpha-blockers \((477.9 \pm 46.9, P > 0.05)\). At 8 weeks after taking combined zolpidem and alpha-blockers, FBC and NBCi increased compared with baseline. NPI decreased compared with baseline, respectively. NUV showed significant change (Fig. 2).

3.5. Uroflowmetry

At 8 weeks after taking combined zolpidem and alpha-blockers, Qmax, voided volume increased and PVR decreased compared with baseline. Qmax showed significant increase (Fig. 3).

3.6. Sleep quality

Global PSQI scores changed from baseline \((8.82 \pm 0.55)\) to 8 weeks after taking zolpidem and alpha-blockers \((7.20 \pm 0.63, P = 0.18)\). Percentage of severe sleep disorders improved from baseline \((30 \text{ of } 39 \text{ patients, } 76.9\%)\) to 8 weeks after taking zolpidem and alpha-blockers \((9 \text{ of } 39 \text{ patients, } 23.1\%)\) (Fig. 4, \(P < 0.01\)). Daytime dysfunction out of seven components decreased significantly from baseline \((1.59 \pm 0.10)\) to 8 weeks after taking combined zolpidem and alpha-blockers \((1.00 \pm 0.15, P < 0.05)\) (Table 1).

3.7. Side-effects

There were no serious side-effects in any patient.
Zolpidem and Alpha-Blocker for Nocturia

4. DISCUSSION

Constant poor sleep can cause excessive daytime sleepiness and dysphoric mood.15 Causes of sleep disruption are sleep apnea, depression, anxiety, primary sleep disorders, cardiac problems and nocturia. Nocturia and worries were the most frequent causes of disturbed sleep in adults over the age of 50 years.16 Causes of nocturia consist of polyuria, nocturnal polyuria, and bladder storage problems. However, in patients with sleep disturbance, nocturia can be secondary to awakening at night rather than nocturnal polyuria.5

Zolpidem is a nonbenzodiazepine hypnotic agent for the treatment of insomnia. Evidence for the utility of currently available nonbenzodiazepine hypnotics points

### Fig. 3
Parameters in uroflowmetry and postvoid residual urine volume (PVR) at baseline and after 8 weeks. *Significant difference by paired t-test.

### Table 1
Improvement of sleep quality using Pittsburgh Sleep Quality Index (PSQI) at 8 weeks after combined zolpidem and alpha-blocker therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Post treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective sleep quality</td>
<td>0.43 ± 0.15</td>
<td>1.10 ± 0.46</td>
<td>0.08</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>1.52 ± 0.14</td>
<td>1.20 ± 0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.77 ± 0.14</td>
<td>1.40 ± 0.31</td>
<td>0.27</td>
</tr>
<tr>
<td>Habitual sleep efficiency</td>
<td>0.98 ± 0.17</td>
<td>0.70 ± 0.26</td>
<td>0.47</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1.50 ± 0.08</td>
<td>1.20 ± 0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>Use of sleep medication</td>
<td>1.07 ± 0.18</td>
<td>0.60 ± 0.27</td>
<td>0.23</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>1.59 ± 0.10</td>
<td>1.00 ± 0.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Global PSQI score</td>
<td>8.82 ± 0.55</td>
<td>7.20 ± 0.63</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Post-treatment means at 8 weeks after taking zolpidem and alpha-blockers.

### Fig. 4
Percentage of severe sleep disorders. *Significant difference by paired t-test.
to their primary efficacy as sleep-onset, rather than as sleep-maintenance, agents. By comparison with benzodiazepines, there has been less evidence of subjective and objective next-day residual effects associated with zolpidem. Zolpidem is effective in the long-term treatment of primary and secondary chronic insomnia with little evidence of tolerance, withdrawal symptoms, or rebound insomnia.

PSQI is a simple, self-administered questionnaire that contains 19 items assessing a wide variety of factors related to sleep quality. The PSQI has Global PSQI Score including seven components such as subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. A global PSQI score over 5 provided a sensitive and specific measure of poor sleep quality relative to clinical and laboratory measure. Furthermore, a global PSQI score over 5 indicates that a subject is having severe difficulties in at least two areas or moderate difficulties in more than three areas. Our results demonstrated that mean global PSQI scores at baseline improved after combined zolpidem and alpha-blocker therapy. Percentage of severe sleep disorders improved more significantly from baseline to 8 weeks after taking zolpidem and alpha-blockers. Daytime dysfunction out of seven components also decreased significantly. Combined zolpidem and alpha-blocker therapy improved sleep quality significantly.

Our results demonstrated that combined zolpidem and alpha-blocker therapy improved nocturia. IPSS is the most commonly used instrument for voiding difficulty including nocturia. At 8 weeks after taking zolpidem and alpha-blockers, storage and voiding symptoms improved. QoL index improved also after 8 weeks of combined zolpidem and alpha-blocker therapy. Our results demonstrated that combination therapy of zolpidem and alpha-blockers resulted in a subjective reduction in nocturia episodes when given to some men with LUTS.

FVCs are the most valid instrument for diagnosing nocturia in elderly men; they have the advantage of being recorded at home in the subject’s environment and without interference of individual daily habits. Nocturia may be caused by nocturnal polyuria and natriuresis in male patients with LUTS. Our results of FVCs showed that nocturia was caused by low bladder volume, polyuria or nocturnal polyuria. Twenty-four-hour urine volume, nocturnal urine volume, and nocturnal polyuria index decreased and functional bladder capacity and nocturnal bladder capacity index increased after taking zolpidem. Improved sleep quality after taking zolpidem may inhibit hypersensitivity of bladder and increase functional bladder capacity and nocturnal bladder capacity index. Recently, it was reported that zolpidem may improve nocturia through an increase in bladder capacity and a decrease in urine excretion. Decrease of 24-h urine volume, nocturnal urine volume and increase of functional bladder capacity and nocturnal bladder capacity index after taking zolpidem may contribute the improvement of voiding symptoms.

Uroflowmetry is one of the objective tools for diagnosing voiding difficulty in elderly men. Our results demonstrated that Qmax and voided volume increased and PVR decreased. There were no serious side-effects in any patient.

There is a limitation that our study is not placebo-controlled; a placebo effect cannot be excluded. However, few reductions in nighttime frequency in the placebo group were reported. Our study includes a small population that does not represent the whole population of sleep disorders or of reduced bladder capacity that respond to zolpidem treatment. Larger studies are indispensable.

In summary, combined zolpidem and alpha-blocker therapy improved an objective reduction in nocturia episodes when given to some men with LUTS unresponsive to alpha-blocker monotherapy in men with LUTS.

Disclosure

The authors declare no conflicts of interest.

REFERENCES